Modern Concepts of Cardiovascular Disease

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TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

Early experiences with penicillin therapy of subacute bacterial endocarditis were discouraging, but as supplies of penicillin have increased and the larger doses of the drug have been used, the picture has changed dramatically. It can now be stated unequivocally that the great majority of patients who have streptococcal endocarditis can be cured with sufficiently intensive administration of penicillin. Of forty-nine patients treated at Presbyterian Hospital, forty-one are living and well with an average follow-up of eighteen months, and of the eight deaths four were due to causes other than uncontrolled infection.

With this change in the therapeutic outlook, the early diagnosis of the disease becomes highly important. One should suspect its presence in any patient with valvular heart disease who has unexplained fever for more than a week. Any of the usual stigmata including heart murmur, fever, embolic phenomena, splenomegaly and anemia may be absent in a given case, especially in the early stages of the disease, and the establishing of the correct diagnosis rests in the last analysis on the repeated finding of positive blood cultures. It is of the utmost importance that, whenever possible, the offending organism be recovered before therapy is started, for only with knowledge of the in vitro sensitivity of the strains to available antibiotics can a rational plan of treatment be formulated.

In approximately 95 per cent of cases subacute bacterial endocarditis is caused by streptococci of either the viridans or anhemolytic variety. The majority of these are susceptible to penicillin, but there is a wide strain variation in this characteristic. Fortunately, growth of 90 per cent of the strains recovered from patients with subacute bacterial endocarditis is inhibited in vitro by 0.1 unit of penicillin per cubic centimeter. For the remaining 10 per cent, however, up to 10 units per cubic centimeter or more may be required to inhibit growth. To date no correlation with serologically or biochemically distinguished types has been shown except that the enterococci or strains of Streptococcus faecalis have proved uniformly highly resistant to penicillin. Development of penicillin resistance by nonhemolytic streptococci occurs very uncommonly even in patients who have repeated relapses.

In general, the correlation between in vitro sensitivity of the infecting organisms to penicillin and the clinical results has been surprisingly good. Strains inhibited by 0.1 unit per cubic centimeter or less have been easily eradicated in most instances. Those requiring up to 0.5 units have been more resistant clinically, and larger doses of the drug have been necessary in treating these infections. When the in vitro sensitivity of the strain is between 0.5 and 10 units, heroic doses are required, but success may be attained with intensive enough therapy. Occasional cases are encountered which prove resistant to treatment beyond what might be expected from the penicillin sensitivity of the organism in vitro. The explanation for this discrepancy is not entirely clear; the duration of the disease, valves involved and the general condition of the patient do not seem to have any bearing. Probably the size of the vegetations is important, but one has no way of estimating this factor except that many patients who have had resistant infection have failed to show the usual embolic phenomena and presumably the size of the vegetations has not been reduced by dislodgement. Loewe has described an organism which he calls "Streptococcus s.b.e." recovered in refractory cases of the disease which he feels is important in differentiating patients who will prove to require larger than usual doses of penicillin for cure of their infection. Not enough data have been published as yet to permit evaluation of these observations.

Therapy

It is generally agreed now that using heparin or dicumarol in conjunction with penicillin in the treatment of subacute bacterial endocarditis is not only unnecessary but is contraindicated because of the danger of hemorrhage. Furthermore, there is no evidence as yet that sulfadiazine or fever therapy contribute to the therapeutic results. Granted that penicillin is the important agent, the problems which arise are mainly concerned with the route of administration, duration of therapy and the criteria for judging progress during treatment. As to the method of administering the drug, there is no clear-cut evidence that one parenteral route is superior to another or that a constant drip is necessary. Many patients have been cured by fractional intramuscular injections every two or three hours, and it seems reasonable to try this method first and to use the more laborious continuous intravenous or intramuscular drips only in cases in which the disease proves refractory.

The daily dosage of penicillin and duration of treatment must vary from patient to patient, but certain general principles can be outlined. At least two to three weeks of uninterrupted therapy should be given; the daily dose should be that which attains average blood levels of four or five times the amount required for in vitro inhibition of the infecting strain. For the average patient, this dose will be between 500,000 and 1,000,000 units per twenty-four hours. If the organism is unusually resistant to penicillin or if relapse occurs after such a course of treatment, much larger doses may be required. As many as five or six relapses have occurred in a few patients who have eventually been cured and returned to useful active lives. The point above all others which deserves emphasis at this time is that

hope of cure should not be abandoned under any circumstances unless the complications of the disease, such as incapacitating heart failure or cerebral embolization, render the patient clearly beyond repair. Doses of penicillin as high as 20,000,000 units a day have cured the infection of some patients in whom many months of therapy with from 2,000,000 to 10,000,000 units daily has failed. The upper limit of human tolerance to penicillin has not yet been established, and it may be that as larger amounts of the drug become available, still higher doses will be found effective in the occasional extremely refractory case.

The clinical course of patients under therapy is so variable as to make prediction of the outcome virtually impossible while penicillin is being administered. Some patients continue to have fever, elevated sedimentation rate, leukocytosis and embolic phenomena for several weeks after treatment is stopped and yet turn out eventually to be cured. Conversely, others appear to be doing beautifully as long as penicillin is administered but relapse shortly after the drug is discontinued. Fortunately relapses almost always occur within two weeks. Our approach has been to treat patients for about three weeks and then to stop more or less irrespective of the clinical condition. If the blood cultures taken during the next two weeks remain sterile, one can be reasonably hopeful that the patient is cured even if everything has not returned to normal. If positive cultures are obtained again, a similar course of treatment with penicillin at a higher daily dosage is recommended. In my experience nothing has been gained in resistant cases by prolonging therapy beyond one month. Valuable time may be lost and one may get a false sense of security while an extended course of two or three months is in progress only to have a relapse occur at the end. Repeatedly patients have been seen who have had several relapses after prolonged courses and have been cured finally by an intensive course of from two to three weeks.

The degree of residual functional damage to the heart after cure of the infection has been surprisingly small in most of my cases. The great majority of patients have returned to full activity. Two patients have gone through pregnancy normally and only a small proportion of them require maintenance on digitalis. Several patients who have appeared to have alarming cardiac damage with mild decompensation during the active stage of the infection have shown unexpected increases in cardiac reserve during convalescence. With the added strain on the heart because of fever, anemia and perhaps focal infection in the myocardium, one may see definite cardiac failure which proves to be completely reversible as the infection is controlled.

It has been established beyond any doubt that a significant proportion of patients acquire bacterial endocarditis as a result of dental procedures, especially extraction of a tooth. For this reason, all patients who have valvular heart disease, either rheumatic or congenital, should be warned that they must never have any dental operations performed except under conditions where adequate prophylactic measures can be instituted. What constitutes a satisfactory prophylactic regimen has not yet been clarified. One patient developed the disease after tooth extraction in spite of full doses of sulfadiazine plus 25,000 units of penicillin every three hours for two days. At present my colleagues and I are giving sulfadiazine plus 100,000 units of penicillin every three hours for forty-eight hours followed by several days of sulfadiazine alone. Whether or not this will prove adequate remains to be seen.

Summary

In summary, it may be said that subacute bacterial endocarditis is a disease fundamentally amenable to cure by chemotherapy and that penicillin has proved the most satisfactory agent so far. Because of the varying sensitivity to penicillin of different strains of nonhemolytic streptococci, it is strongly recommended that the sensitivity of the organism be determined in each individual case. The dosage necessary to effect cure of the disease varies widely from case to case depending primarily on the susceptability of the infecting strain. With intensive and persistent therapy, it is possible to cure the infection in almost every patient, although at times as much as 20,000,000 units a day may be required.

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